IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Jacques DUMAS et al.		Confirmation No.:	9096
Serial No.:	09/838,286	Examiner:	KWON, Brian Yong S.
Filed:	April 20, 2001	Group Art Unit:	1614

Title: HETEROARYL UREAS CONTAINING NITROGEN HETERO-ATOMS AS P38 KINASE INHIBITORS

BRIEF ON APPEAL

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on September 28, 2006 , please consider the following remarks.

The attached check includes the fee of $500.00 as set forth under § 41.20(b)(2) and the fee of $1,590.00 for a four-month extension of the period to respond. The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

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(i) REAL PARTY IN INTEREST

The real party in interest is: BAYER PHARMACEUTICALS CORPORATION, 400 Morgan Lane, West Haven, Connecticut 06516, United States of America, a corporation organized under the laws of the State of Delaware, United States of America.

(ii) RELATED APPEALS AND INTERFERENCES

There are no pending appeals or interferences on subject matter directly related to this application.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Services as First Class Mail in an envelope addressed to: Commissioner of Patents, P O Box 1450, Alexandria, VA 22313-1450 on: January 29 2007
Name: Richard J Traverso
Signature: [signature]

(iii) STATUS OF CLAIMS

Claims 26 and 39-74 are pending in the present application.

Claims 26, 39-49, 51 and 57-74 are withdrawn from consideration following an election of species requirement.

Claims 50 and 52-56 are rejected and are on appeal. These claims appear in the attached Appendix.

(iv) STATUS OF AMENDMENTS

No amendments were filed or proposed after the final rejection.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention is directed to methods for treating a disease mediated by the enzyme p38 within a host by administering a diaryl urea of Formula I: A-D-B (I); or a pharmaceutically acceptable salt thereof. (See page 7, line 29 to page 8, line 1.) The entity D represents a urea moiety (see page 8, line 5) and entity A is a specific heteroaryl moiety selected from t-butylpyridinyl, (trifluoromethyl) pyridyl, isoquinolinyl or quinolinyl, which can be substituted or unsubstituted (see page 8, line 6; page 13, line 28-30 and page 14, lines 2-3). Entity B is selected from a group of substituted or unsubstituted aryl moieties, hetaryl moieties or is a bridged cyclic structure of the formula $-L\ (ML^1)_q$, wherein q is an integer of 1-3, L^1 and L are each independently selected from a group of aryl or hetaryl moieties and M is bridging group such as –O-, $-CH_2-$ and -S-. (See page 8, lines 10-20, page 13, lines 3-7, and page 13, lines 14-17.) The substituents for these moieties are defined in claims 50 and 52-53. (see page 10, lines 24-28, page 14, lines 29-30, page 11, lines 1-2, and page 13, lines 18-20). Claim 54 is directed to salt forms of the compounds of formula I (see page 17, lines 6-21). The treatment of diseases other than cancer are preferred and preferred methods treat the diseases recited in claim 56 and on pages 6 and 7 of the specification, such as rheumatoid arthritis, osteoarthritis, septic arthritis, and corneal ulceration.

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds for rejection to be reviewed are:

(1) the rejection under 35 U.S.C. § 112, first paragraph, i.e., whether claims 50, 52-56 directed to methods for the treatment of diseases mediated by p38 within a host are enabled.

(vii) ARGUMENT

Method claims 50, 52-55 are directed to treating diseases "mediated by p38" using the compounds of formula I. The functional definition used to define the diseases is commensurate in scope with the p38 kinase activity of the compounds of formula I, which is demonstrated by the results (IC_{50} values) of the in-vitro p38 kinase assay disclosed in the specification on page 74 and confirmed by the in-vivo p38 kinase assay disclosed on page 75 of the specification. Method claim 55 further defines the diseases to be treated as "other than cancer," and method claim 56 further defines specific diseases. Therefore, claims 55 and 56 are narrower scope.

The specification cites a number of publications on pages 2-5, which are representative of the state of the art at the time of the invention. These publications have correlated TNFα production and MMP production with a number of diseases. Since inhibition of p38 leads to the inhibition of TNFα and MMP production, the p38 inhibitors of this invention will be useful in treating these diseases. It is acknowledged in the office action dated June 28, 2006, that the specification is enabling for treating specific diseases mediated by p38, (i.e. rheumatoid arthritis, osteoarthritis and septic arthritis) by specific compounds of formula I. No evidence has been presented which even suggests that any compounds of this invention, as inhibitors of p38, would not be effective in treating the diseases defined by the functional language. Furthermore, no evidence has been presented of the "undue experimentation," allegedly necessary to practice the invention commensurate in scope with the claims. The publications cited in the June 28, 2006 office action do not support the conclusions and allegations made in rejecting claims 50, 52-56.

The allegation that "the art recognizes that the inhibition of p38 is not useful for the treatment of asthma," overstates the conclusion and showing made in the publication by Chialda et al. Respiratory Research 2005, 6:36, pp1-19. Chialda tests only one p38 inhibitor, SB203580 and one JNK inhibitor, SP600125, in comparing the inhibition of two signaling

pathways in treating asthma. The JNK inhibitor was shown to be more effective such that the paper concludes in the Abstract, "These results demonstrate that the MAPKs, ERK and JNK may be suitable targets for anti-inflammatory therapy of asthma, whereas inhibition of p38 seems to be an unlikely target." In comparing the agents, Chialda et al. do not indicate the use of p38 inhibitors in treating asthma is ineffective, only that the inhibitors of another pathway, JNK inhibitor, was more effective. More importantly, the disclosure in this article does not represent the state of the art. Many investigators have found p38 effective in treating asthma. See, for example, Duan et al., "Inhaled p38α Mitogen-activated Protein Kinase antisense Oligonucleotide Attenuates Asthma in Mice", Am. J. Respir. Crit. Care Med. Vol. 171, pp.671-578, 2005.

Similarly, Kapoun et al. do not teach that p38 inhibitors are ineffective in treating pulmonary fibrosis in their Abstract, Molecular Pharmacology, 2006, www.molpharmaspetjournals.org. They state, "These studies also revealed that while the p38 pathway may not be needed for appearance or disappearance of the myofibroblast, it can mediate a subset of inflammatory and fibrogenic events of the myofibroblast during the process of tissue repair and fibrosis."

Feldmann, also does not teach that p38 inhibitors are ineffective in treating inflammation or other conditions in the article: Nature Immunology, 2001, vol 2, No.9 pp.771-773. By stating that, "Despite the fact that drugs blocking p38 are effective in animal models, human studies so far have been hindered by drug toxicity," Feldman does not indicate that these drugs are ineffective in humans and more importantly, does not show or suggest the compounds used in the methods claimed herein are toxic. The teachings within the articles by Chialda et al., Kapoun et al., and Feldmann provide no facts or suppositions which support the rejection.

It is alleged that the invention is extremely complex in that it encompasses anticipating multiple complex disorders having unrelated manifestations and sequentially administering the instant compounds. It is also alleged that, "There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated through p38 or (ii) all types of diseases other than cancer that are mediated by p38." Appellants wish to draw attention to US Patent No. 5,932,576, which contains claims to treating p38 mediated diseases using other small molecule compounds. The

inventors of the '576 patent disclose the ability of the named compounds to inhibit p38 through in-vitro and in-vivo assays, as do the Appellants in their application. Others have defined the treatment of numerous inflammatory diseases using functional language similar to that used here. For example, US Pat. Nos. 5,593,991 and 5,593,992 claim the treatment of "cytokine mediated diseases," with small molecules, the activity of which is demonstrated by in-vitro assays. See also US Patent 5,658,903, claim 12. Therefore, contrary to this allegation, those skilled in the art have recognized and claimed that certain compounds can be effective for treating all types of diseases mediated by p38.

Even if these allegations regarding the prior art were true, they are not relevant to the issue of enablement. As discussed in Wands, cited by the Examiner, a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." No evidence has been presented that the specification is deficient in this regard. Again, only unsupported allegations are made that undue experimentation is necessary to practice the invention.

The specification provides ample guidance as to how to prepare pharmaceutical compositions with the compounds of this invention and how to administer these compositions in the treatment of the diseases mediated by p38 (see pages 22-26). The specification also provides dosage ranges for the various methods of administration (see pages 26-27). In fact, the specification provides more than it needs to, e.g., in vitro p38 kinase assays (and IC_{50} data) and in vivo assays. In similar fashion, one of ordinary skill in the art, by performing the same or similar tests, can, by routine experimentation, determine the activity levels of each of the claimed compounds in treating various p38 mediated diseases. This is absolutely routine in the field. Thus, Appellants have provided more than adequate guidance (and examples) to enable the claimed invention. Given the extent of the disclosure provided, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat any one of the recited diseases with a compound of this invention. Certainly the step of administering the instant compounds does not require undue experimentation and the large number of diseases already correlated with TNFα production and MMP production do not require undue experimentation to be identified.

In re Buting, 163 USPQ 689 (CCPA 1969), is cited for the principal that "evidence

involving a single compound is insufficient to establish the utility of claims to disparate types of cancers." The state of the art of cancer treatment has advanced significantly in 35 years and, as shown by the citations on pages 3-5 of the specification, there is evidence suggesting these compounds will be effective in treating more than one disease. While the various types of diseases are seemingly unrelated, they are linked in that they are recognized as being mediated by p38. Without any supporting evidence or scientific basis, the conclusion is made, "it is beyond the skill of oncologists today to get an agent to be effective against all cancers or cancers mediated by p38." The disclosures in US Patent Nos. 5,932,576; 5,593,991 and 5,593,992, which are mentioned above, suggest otherwise.

It is alleged that administering a compound of formula I is highly unpredictable in regard to therapeutic effects, side effects and toxicity. In making this allegation, there is an assumption that the application is required to meet clinical standards as set by the FDA to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. Proof relating to toxicity, side effects and therapeutic effects requires a showing of efficacy and safety, which is beyond what is necessary to satisfy the enablement requirement of 35 USC §112, first paragraph. An applicant is not required to test the claimed compounds in their final use to satisfy the enablement requirement of 35 USC §112, first paragraph. As stated in In re Brana, 51 F.3d 1560, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995) with respect to the utility requirement,

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Scott, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs will prevent any companies from obtaining patent protection on the promising new invention, thereby eliminating an incentive to pursue, through research and development, potential cures in any crucial area such as the treatment of cancer.

Although directed to the issue of utility, this rationale translates to prescribing the disclosure necessary to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

Page 51 of the text "Goodman and Gilman," regarding drug interactions, is cited in the office action . The claims of this application do not require that the compounds of formula I be co-administered with any other drug and drug-drug interactions discussed in this text should not

be an issue in their use. When co-administration with another drug is necessary, there is no evidence that the compounds of formula I will not be effective or that potential interactions can not be dealt with in a routine manner.

It is alleged that the guidance given by the specification as to what types of ureas would be useful in a method of the instant invention is limited. The specification indicates at page 7, lines 24 -30 that, the present invention, provides "a method for treating of p38-mediated disease states in humans or mammals, e.g., disease states mediated by one or more cytokines or proteolytic enzymes produced and/or activated by a p38 mediated process. In these methods a compound of formula I, or a pharmaceutically acceptable salt thereof, is administered." This language is clear in meaning and provides sufficient guidance to satisfy the statute with respect to the methods of claims 50 and 52-56.

No deficiencies have been identified in the assays provided within the disclosure to show p38 activity. In addition, the party in interest is a pharmaceutical manufacturer which would logically only use assays that were reasonably correlated with efficacy to find new products. However, it is alleged, "the specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for the treatment of all of the claimed disease conditions that are mediated by p38. Appellants submit the specification provides an objectively enabling disclosure and there is no need for additional evidence or tests to satisfy the statute.

It is also alleged that one skilled in the art would be forced to search for embodiments that have p38 activity and determine which compounds treat all of the diseases mediated by p38 and that the skilled artisan would not know which compounds are capable of accomplishing the desired result without undue experimentation.

Clearly the specification identifies that compounds of formula I are active inhibitors of p38 and the compounds of formula I are clearly defined such that a search for active compounds is unnecessary. As discussed above, the specification provides ample guidance as to how to prepare and use pharmaceutical compositions with the compounds of formula I in the treatment of the diseases mediated by p38 to satisfy the enablement requirement. Additionally, the enablement requirement is satisfied if, given what those of ordinary skill in the art already know, the specification teaches those in the art enough that they can make and use the claimed invention without "undue experimentation." See Amgen v Hoechst Marion

Roussel, 314 F.2d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). The use of any of the claimed compounds to treat a p38 mediated disease would be routine for those of ordinary skill in the art in view of Appellants' disclosure.

It is alleged in the office action that there are no known compounds of similar structure to those of Formula I which have been demonstrated to treat all types of diseases mediated by p38. Appellants note that US Patent No. 6,800,626, discloses one example of a group of related compounds which treat all types of p38 mediated diseases. Over 25 types are claimed in the patent (See claims 16-18).

The publication by Dumas et al., Bioorganic & Medicinal Chemistry Letters, 10, 2000, 2047-2050, is cited in the office action as evidence that the activity of the claimed compounds is unpredictable in that Dumas et al. show that modification of the urea core group of the compounds disclosed results in different physiological activity. The compounds of formula I herein have specific heteroaryl groups defined by moiety "A", which are predictive of p38 activity, and also distinguish the compounds disclosed by Dumas et al. If one skilled in the art needed to determine the level of p38 inhibition for a particular compound, this task would be routine in view of the assays provided in the specification and others which were known in art at the time of this invention.

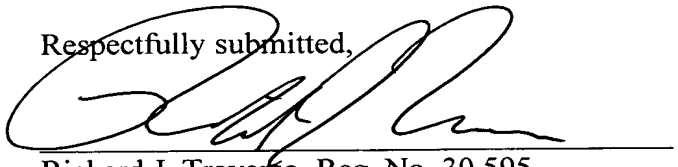
Appellants have provided examples of compounds of formula I in the specification and tested their activity reven though there is no requirement that an applicant provide any working examples to satisfy the statute. See, for example, Marzocchi, supra, stating that how "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02. Since the statute does not require any examples, Appellants need not illustrate the activity of every embodiment to enable the subject matter of claims 50 and 52-56. "An inventor need not ... explain every detail since he is speaking to those skilled in the art," In re Howarth, 654 F.2d 105, 210 U.S.P.Q. 689 (CCPA 1981). "Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be," In re Gay, 309 F.2d 769, 774, 135 U.S.P.Q 311 (CCPA 1962).

For the reasons stated above, Appellants respectfully submit the subject matter of the claims on appeal satisfy the requirements of 35 U.S.C. §112, first paragraph, and the PTO has failed to meet its burden of establishing otherwise. Therefore, Appellants respectfully request the outstanding rejection be reversed.

Double Patenting

The provisional obviousness type double patenting rejections based on copending application nos. 09/776,935 and 10/086,417 are not ripe for appeal in that subject matter, which is other wise allowable, has not been identified in this application.

Respectfully submitted,



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Attorney Docket No.: Bayer -0014

Date: January 29, 2007

(xi) APPENDIX OF CLAIMS ON APPEAL

50. A method of treating a disease mediated by p38 within a host, said method comprising administering to said host a compound of Formula I:

A - D - B (I)

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a

substituted t-butylpyridinyl, unsubstituted t-butylpyridinyl, substituted (trifluoromethyl)pyridyl, unsubstituted (trifluoromethyl)pyridyl, substituted isoquinolinyl, unsubstituted isoquinolinyl, substituted quinolinyl or unsubstituted quinolinyl, and

B is a substituted or unsubstituted, phenyl naphthyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl or a bridged cyclic structure of the formula $-L(ML^1)_q$, wherein q is an integer of 1-3, and L^1 and L are each independently thiophene, substituted thiophene, phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, quinolinyl substituted quinolinyl, isoquinolinyl or substituted isoquinolinyl and M is –O-, $-CH_2-$, -S-, -NH-, -C(O)-, $-O-CH_2-$ or $-CH_2-O-$, with cyclic structure L bound directly to D,

wherein the substituents for A are selected from the group consisting of halogen, up to per-halo, and Wn, where n is 0-3 and each W is independently selected from the group consisting of

C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having at least a five cyclic members and 0-3 heteroatoms selected from N, S and O; C_{2-10} alkenyl, C_{1-10} alkenoyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_3-C_{12} heteroaryl having at least 5 cyclic members and 1-3 heteroatoms selected from O, N and S, C_4-C_{24} alkheteroaryl having at least 5 cyclic members and 1-3 heteroatoms selected from O, N and S;

substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from N, S and O; substituted C_{2-10} alkenyl, substituted C_{1-10} alkenoyl, substituted C_6-C_{14} aryl, substituted C_7-C_{24} alkaryl, substituted C_7-C_{24}

aralkyl, substituted C_3-C_{12} heteroaryl having at least 5 members and 1-3 heteroatoms selected from O, N and S, substituted C_4-C_{24} alkheteroaryl having at least 5 members and 1-3 heteroatoms selected from O, N and S,

-CN, $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$, $-NR^7C(O)OR^{7'}$, $-NR^7C(O)R^{7'}$, with each R^7 and $R^{7'}$ independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{2-10} alkenyl, C_{1-10} alkenoyl, up to per halosubstituted C_{1-10} alkyl, up to per halosubstituted C_{1-10} alkoxy, up to per halosubstituted C_{2-10} alkenyl and up to per halosubstituted C_{1-10} alkenoyl, C_3-C_{10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_3-C_{10} hetaryl having at least 6 cyclic members and 0-3 heteroatoms selected from O, S and N, up to per halo substituted C_3-C_{10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from O, S and N, up to per halo substituted C_6-C_{14} aryl and up to per halo substituted C_3-C_{10} hetaryl having at least 6 cyclic members and 0-3 heteroatoms selected from O, S and N,

where W is a substituted group, it is substituted by halogen, up to per halo, or by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$, $-NR^7C(O)OR^{7'}$, and $-NR^7C(O)R^{7'}$, wherein R^7 and $R^{7'}$ are independently as defined above;

wherein the substituents for B are selected from the group consisting of halogen, up to per-halo, and J_n, where n is 0-3 and each J is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$, $-NR^7C(O)OR^{7'}$, $-NR^7C(O)R^{7'}$, with each R^7 and $R^{7'}$ independently as defined for W above, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having at least five cyclic members and 0-3 heteroatoms, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-14} aryl, C_{3-12} hetaryl having at least a five cyclic members and 1-3 heteroatoms selected from N, S and O, C_{7-24} aralkyl, C_{7-24} alkaryl, C_4-C_{23} alkylheteroaryl having at least six members and 1-3 heteroatoms selected from O, N and S, substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl having at least a five-members and 0-3 heteroatoms selected from N, S and O, substituted C_{2-10} alkenyl, substituted C_{1-10} alkenoyl, substituted C_6 - C_{14} aryl, substituted C_{3-12} hetaryl having at least five cyclic members and 1-3 heteroatoms selected from N, S and O, substituted C_{7-24} alkaryl, substituted C_7-C_{24} aralkyl and substituted C_4-C_{23} alkylheteroaryl having at least six members and 1-3 heteroatoms selected from O, N and S,

where J is a substituted group, it is substituted by halogen, up to per halo, or by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^{7'}$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^{7'}$, $-NR^7C(O)R^{7'}$, and $-NR^7C(O)OR^{7'}$, with R^7 and $R^{7'}$ as defined above for W.

52. A method of claim 50, wherein A has 1-3 substituents selected from the group consisting of C_{1-10} alkyl, up to per halo substituted C_{1-10} alkyl, -CN, -OH, halogen, C_{1-10} alkoxy, up to per halo substituted C_{1-10} alkoxy and C_{3-10} heterocyclic moieties having at least 5 cyclic members and 1 to 2 heteroatoms selected from the group of consisting of nitrogen, oxygen and sulfur.

53. A method of claim 50 wherein L^1 is substituted 1 to 3 times by one or more substituents selected from the group consisting of -CN, halogen up to per halo, C_{1-10} alkyl, C_{1-10} alkoxy,-OH, up to per halo substituted C_{1-10} alkyl, up to per halo substituted C_{1-10} alkoxy, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$ $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)R^7$ or $-NO_2$, wherein each R^7 and $R^{7'}$ is independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{2-10} alkenyl, C_{1-10} alkenoyl, up to per halosubstituted C_{1-10} alkyl, up to per halosubstituted C_{1-10} alkoxy, up to per halosubstituted C_{2-10} alkenyl and up to per halosubstituted C_{1-10} alkenoyl.

54. A method of claim 50 wherein a pharmaceutically acceptable salt of a compound of formula I is administered which is selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluorosulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

55. A method as in claim 50 for the treatment of a disease other than cancer.

56. A method as in claim 50 wherein the condition within a host treated by administering a compound of formula I is rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophobic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, tempero mandibular joint disease or demyelating disease of the nervous system.

(ix) EVIDENCE APPENDIX

None

(x) RELATED PROCEEDINGS APPENDIX

None